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Asymmetric Synthesis of (−)-Swainsonine

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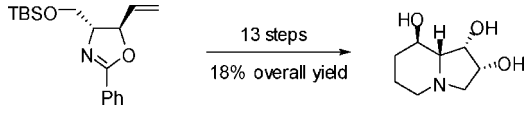
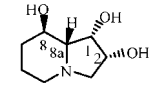


We report a new asymmetric synthetic method for (−)-swainsonine utilizing a chiral oxazoline precursor. The key features in this strategy are the diastereoselective oxazoline formation reaction catalyzed by palladium(0), diasteroselective dihydroxylation, and the stereocontrolled allylation reaction with $TiCl_4$.

(−)-Swainsonine was first isolated from the fungus *Rhizoctonia leguminicola* in 1973[1] and later found in several plants and fungi.[2] (−)-Swainsonine (**1**, Figure 1) exhibits lysosomal α-mannosidase and mannosidase II inhibitory properties[3] and has been tested as a treatment for cancer, HIV, and immunological disorders.[4] (−)-Swainsonine was the first glycoprotein processing inhibitor to be selected for clinical testing as an anticancer drug, reaching phase II clinical trials.[5] A number of synthetic approaches have been reported due to its novel indolizidine structure and its promising biological activity.[6]

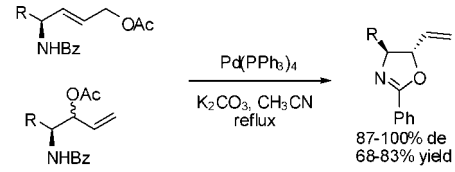
Over the past several years, we have been investigating the stereoselective intramolecular cyclization of homoallyl benzamide through a π-allylpalladium complex catalyzed by Pd(0)



(-)-Swainsonine (1)

FIGURE 1. The structure of (−)-swainsonine.

SCHEME 1. Palladium-Catalyzed Oxazoline Formation



R = (a) $C_6H_5CH_2$, (b) $(CH_3)_2CH$, (c) $(CH_3)_2CHCH_2$, (d) $C_6H_{11}CH_2$, (e) CH_2OTBS

(Scheme 1).[7] We have also been exploring the utility of enantiopure oxazoline as a chiral building block for the stereocontrolled synthesis of natural products.[8] As part of this program, we have developed a novel strategy for stereoselective synthesis of (−)-swainsonine. Herein we describe the novel asymmetric synthesis of (−)-swainsonine utilizing an oxazoline as a chiral building block.

As shown in Scheme 2, our retrosynthetic analysis suggested that (−)-swainsonine (**1**) could be synthesized by mesylation, hydrogenolysis, and deprotection of **2**. Also, it was anticipated that **3** could be converted to **2** in two steps (mesylation and cyclization).

We focused our initial efforts upon the enantioselective synthesis of the primary alcohol **3**, hypothesizing that it would be accessible via the protection and oxidation of the *anti*-amino alcohol **4**.

The primary alcohol **5** would be converted to the aldehyde, which would then be employed in diastereoselective *anti*-amino alcohol formation by using $TiCl_4$-mediated allyltrimethylsilane addition. The primary alcohol **5** could be synthesized by diastereoselective dihydroxylation of the *syn*-amino alcohol **6**,

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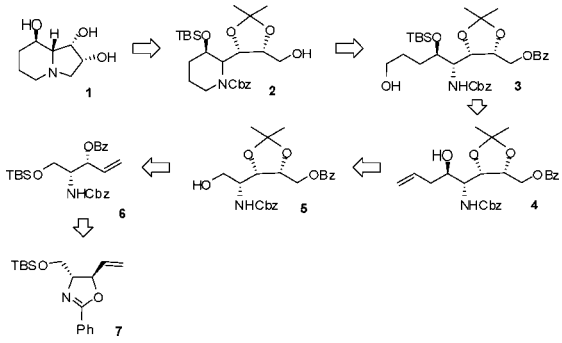
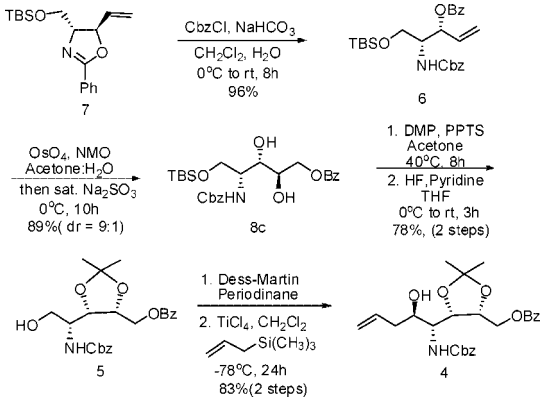
SCHEME 2. Retrosynthetic Analysis



SCHEME 3



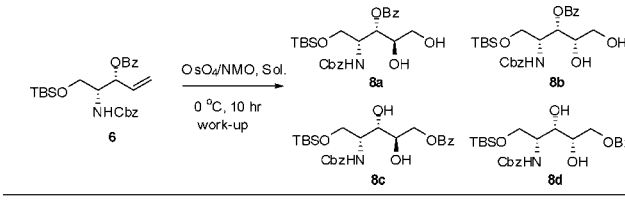
which could be synthesized by ring cleavage of *trans*-oxazoline **7** under Schotten−Baumann conditions. The *trans*-oxazoline **7** was made from D-serine according to known procedures.[8e] Oxazoline could then be utilized to set the vicinal amino alcohol stereochemistry of (−)-swainsonine.

The synthesis of **1** commenced with *trans*-oxazoline **7** as shown in Scheme 3. The *trans*-oxazoline **7** was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate,[9] affording the carbamate **6** in 96% yield. In the next step, diastereoselective dihydroxylation of **6** was attempted with a catalytic amount of osmium tetraoxide in the presence of 1.5 equiv of *N*-methylmorpholine *N*-oxide as the reoxidant (OsO_4/NMO).[10] As expected, the approach of the oxidant took place from the least hindered site to give **8a** as the predominant product. The selectivity was dramatically improved through solvent selection; use of acetone/H_2O (10/1) resulted in a 9:1 mixture of the diastereoisomers **8a** and **8b** in 91% yield.

Interestingly, treatment of the reaction mixture with sat. aqueous Na_2SO_3 caused the benzoyl group of **8a** and **8b** to migrate to the primary alcohol position. The minor product **8d** was easily separated by silica gel chromatography. The results are summarized in Table 1.

Oxidation of alcohol **5** with Dess−Martin periodinane[11] gave the corresponding aldehyde, which was subsequently reacted with allyltrimethylsilane in the presence of 1.0 equiv of $TiCl_4$ at −78 °C to give adduct *anti*-amino alcohol **4** with low diastereoselectivity (4:1 mixture of *anti*/*syn* isomer; entry 2, Table 2).[12]

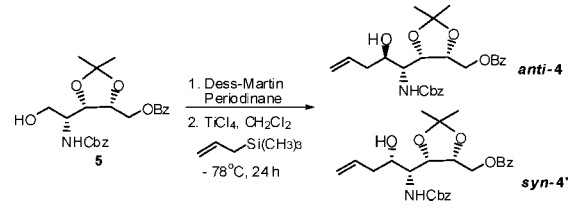
TABLE 1. Diastereoselective Dihydroxylation of 6



entry	solvent	workup	yield[a] (%)	ratio[b]
1	CH_2Cl_2/H_2O	15% $Na_2S_2O_3$	91	**8a/8b** = 4:1
2	acetone/H_2O	15% $Na_2S_2O_3$	91	**8a/8b** = 9:1
3	CH_2Cl_2/H_2O	sat. Na_2SO_3	89	**8c/8d** = 4:1
4	acetone/H_2O	sat. Na_2SO_3	89	**8c/8d** = 9:1

[a] Yields refer to the isolated and mixture products. [b] Ratio was determined by ^{1}H NMR analysis of the crude mixture after workup.

TABLE 2. Diastereoselective Allylation Reaction



entry	molar equiv of $TiCl_4$	dr[a] (*anti* 4:*syn* 4′)	yield[b] (%)
1	0.8	1:2	45
2	1.0	4:1	63
3	1.2	8:1	62
4	1.5	15:1	83
5	1.8	7:1	70
6	2.0	5:1	65
7	2.2	3:1	43

[a] Ratio was determined by ^{1}H NMR on the basis of the ratio of **9** and **9′**. [b] Yields refer to the isolated and mixture products.

The yield and the diastereoselectivity were improved to 83% and 15:1 when the amount of $TiCl_4$ was increased to 1.5 equiv (entries 2, 3, and 4). When excess $TiCl_4$ (1.8, 2.0, and 2.2 equiv) was employed, the yields and diastereomeric ratios decreased (entries 5, 6, and 7).

Through extensive examination of various experimental conditions, we established that the reaction of 1.0 equiv of aldehyde and 1.5 equiv of $TiCl_4$ with 1.5 equiv of allyltrimethylsilane formed *anti*-amino alcohol **4** with 15:1 diastereoselectivity in 83% yield after silica gel chromatography.

On the basis of the results of the above experiments, the quantity of $TiCl_4$ is clearly an important factor in controlling the course of the reaction. In the case of entry 4, it is interesting to note that high *anti* selectivity (15:1) was obtained in the reaction with 1.5 equiv of $TiCl_4$.

This stereoselectivity apparently arises from the β-chelated conformer (**A**), which is characteristic of an aldehyde with β-alkoxy groups;[12a] in such cases, β-chelation (**A**) is more effective than α-chelation (**B**) (Figure 2).

A mixture of *anti*-**4** and *syn*-**4′** could not the separated by chromatography. To verify the stereochemical outcome of the

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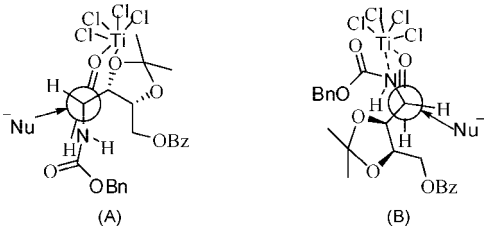


FIGURE 2. β-Chelation (**A**) and α-Chelation (**B**) Conformer.

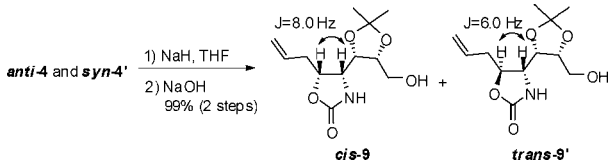


FIGURE 3. *J* values between 4-H and 5-H in 4,5-disubstituted oxazolidin-2-ones.

newly generated stereocenter, these isomers were converted to the corresponding 4,5-disubstituted oxazolidin-2-ones under basic conditions (NaH and then NaOH). Mixtures of *cis*-**9**/*trans*-**9′** were readily separable by chromatography (Figure 3).

The *anti*/*syn* stereochemistry of **4** and **4′** was assigned on the basis of the stereochemistry of the corresponding 4,5-disubstituted oxazolidin-2-ones.

The coupling constants between 4-H and 5-H of the derivatives are known to be *cis* > *trans*.[12c,13] The *J* value ($J_{4,5}$ = 8.0 Hz) observed in the major isomer clearly indicates that this compound possesses the assigned *cis* structure.

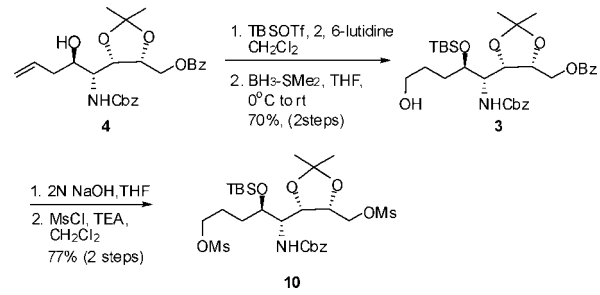
The protection of the resulting alcohol **4** by TBSOTf and subsequent oxidation of the alkene with borane−methyl sulfide gave the corresponding alcohol **3** in 70% yield (Scheme 4).

Hydrolysis of the benzoyl group with 2N NaOH and subsequent mesylation of the corresponding diol gave **10** in 77% yield. With the precursor in hand, we predicted that cyclization would lead to the desired transformation, but exposure of **10** to several reagents [$Pd(OH)_2$, Pd-C, etc.] proceeded sluggishly under various conditions (K_2CO_3 or NaOH in MeOH).[14a]

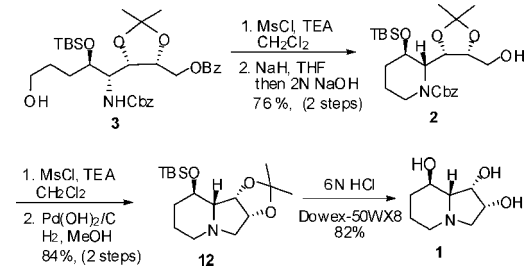
After the mesylation of **3**, exposure of the corresponding mesylate at room temperature to NaH and then to 2 N NaOH led to intramolecular cyclization and then benzoate hydrolysis providing **2** in 76% yield (Scheme 5).[14b,15]

Mesylation of **2** ($MeSO_2Cl$, Et_3N, 0 °C) gave mesylate in excellent yield (95%). Hydrogenolysis of a EtOH/AcOH solution of mesylate (70 psi of H_2 gas) afforded the protected (−)-swainsonine (**12**). Finally, acidic hydrolysis of the protection groups afforded (−)-swainsonine (**1**) in 82% yield after Dowex-50WX8−100 (H^+ form) ion-exchange chromatography. The spectroscopic (^{1}H and ^{13}C NMR) data for synthetic **1** were

SCHEME 4



SCHEME 5



identical with those of synthetic (−)-swainsonine, and the physical properties of **1** {mp 140−142 °C, $[\alpha]^{25}_D$ −82.6 (*c* 1.03, MeOH)} showed good agreement with those reported.[6g]

In conclusion, the potent mannosidase inhibitor (−)-swainsonine (**1**) was synthesized from *trans*-oxazoline **7** as a chiral building block. The net result was synthesis from a linear sequence of 13 steps from the oxazoline **7** in 18% overall yield.

Our approach features the use of *trans*-oxazoline to install the stereocenters at C1 and C8a and makes use of diastereoselective dihydroxylation to utilize the stereocenter at C2. $TiCl_4$-promoted allylsilane addition adjusted the stereochemistry at C8 and provided the allyl group, which could be converted to the appropriate alcohol for ring construction. The key features in this strategy are the diastereoselective oxazoline formation reaction catalyzed by palladium(0), diastereoselective dihydroxylation, and the stereocontrolled allylation reaction with $TiCl_4$.

Experimental Section

(2*S*,3*R*)-Benzyl 3-(*tert*-Butyldimethylsilyloxy)-2-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidine-1-carboxylate (2). A solution of the homoallylic alcohol **3** (1.30 g, 2.16 mmol) and triethylamine (0.66 mL, 4.75 mmol) in dry CH_2Cl_2 (70 mL) was treated with methanesulfonyl chloride (0.35 mL, 4.54 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h (from 0 °C to rt) and diluted with diethyl ether. The organic layer was separated and washed with water and brine. After drying (Na_2SO_4) and concentration in vacuo, the residue was purified over silica gel to give a pure mesylated product. A solution of the mesylated product (1.38 g, 2.03 mmol) in THF (200 mL) at 0 °C was treated with NaH (60% dispersion in oil, 0.24 g, 6.09 mmol, 3.0 equiv) in several portions over 15 min. After 3 h, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with EtOAc (4 × 100 mL) and concentrated. The residue was dissolved in MeOH (10 mL) and then stirred with 2 N NaOH (10 mL) at rt for 2 h and concentrated. The residue was extracted with EtOAc (4 × 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified over silica gel chromatography (ethyl acetate/hexane = 2:1) to give **2** (0.94 g, 90%) as a colorless oil: $[\alpha]^{25}_D$ +33.46 (*c* 1.0, $CHCl_3$); IR (neat)

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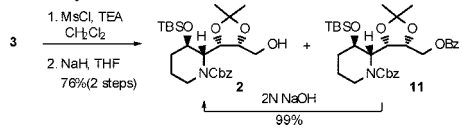
(15) After the mesylation of **3**, the reaction mixture was treated with NaH to afford a 85:15 mixture of **2** and **11** in 76% yield. **11** was reacted with NaOH to afford **2** in 99% yield.



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2930, 1687, 1526, 1461, 1258, 1041 cm^{-1}. **Rotamer**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3 × 0.55H), 0.04 (s, 3 × 0.55H), 0.06 (s, 3 × 0.45H), 0.09 (s, 3 × 0.45H), 0.86 (s, 9 × 0.55H), 0.88 (s, 9 × 0.45H), 1.36 (br, 3H), 1.40 (br, 3 × 0.55H), 1.46 (br, 3 × 0.45H), 1.67−1.77 (m, 2H), 1.83−2.06 (m, 2H), 2.91−2.97 (m, 0.55H), 3.19−3.25 (m, 0.45H), 3.57−3.64 (m, 1H), 3.68−3.76 (m, 1.55H), 3.80−3.82 (m, 0.45H), 4.05−4.08 (m, 0.45H), 4.11−4.14 (m, 0.55H), 4.19−4.23 (m, 1H), 4.32−4.37 (m, 0.55H), 4.35−4.40 (m, 1H), 4.48−4.53 (m, 0.45H), 5.00−5.03 (d, J = 12.5 Hz, 0.55H), 5.14−5.16 (d, J = 12.5 Hz, 0.45H), 5.18−5.21 (d, J = 12.5 Hz, 0.45H), 5.26−5.29 (d, J = 12.5 Hz, 0.55H), 7.28−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.4, 19.1, 19.2, 25.7, 25.8, 25.9, 28.3, 39.4, 56.3, 61.7, 66.0, 67.1, 73.3, 75.1, 108.5, 127.8, 127.9, 128.0, 128.5, 128.6, 137.3, 156.7; HRMS calcd for $C_{25}H_{41}NO_6Si$ (M + 1)480.2781, found 480.2780.

(3a*R*,9*R*,9a*S*,9b*S*)-9-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyloctahydro-[1,3]dioxolo[4,5-*a*]indolizine (12). A solution of the homoallylic alcohol **2** (808 mg, 1.68 mmol) and triethylamine (0.52 mL, 3.70 mmol) in dry CH_2Cl_2 (56 mL) was treated with methanesulfonyl chloride (0.27 mL, 3.54 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h (from 0 °C to rt) and diluted with diethyl ether. The organic layer was separated and washed with water and brine. After drying (anhydrous sodium sulfate) and concentration in vacuo, the residue was purified over silica gel to give a pure mesylated product. To a solution of the above mesylated product (932 mg, 1.67 mmol) in EtOH/AcOH (8 mL, v/v = 9:1) was added $Pd(OH)_2/C$ (100 mg) and the mixture was shaked on a parr apparatus under hydrogen at a 70 psi pressure for 3 days at room temperature. The catalyst was filtered off through a short pad of Celite and concentrated under reduced pressure. The resulting crude product was purified by using silica gel flash chromatography eluting with 10% MeOH/$CHCl_3$ to give protected swainsonine **12** (530 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ +15.92 (*c* 1.0, $CHCl_3$); IR (neat) 3420, 2937, 1651, 1462, 1379, 1197, 840, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.09−0.11 (m, 3H), 0.90 (s, 9H), 1.17−1.29 (m, 1H), 1.30 (s, 3H), 1.49 (s, 3H), 1.58−1.64 (m, 3H), 1.82 (dd, J = 4.0, 5.5 Hz, 1H), 1.95 (dd, J = 4.0, 12.0 Hz, 1H), 2.08 (dd, J = 4.5, 10.5 Hz, 1H), 2.96 (dt, J = 4.5, 10.7 Hz, 1H), 3.12 (d, J = 10.5 Hz, 1H), 3.80 (ddd, J = 4.7, 8.8, 10.7 Hz, 1H), 4.55 (dd, J = 4.5, 6.0 Hz, 1H), 4.61 (dd, J = 4.5, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.3, 18.3, 24.3, 24.9, 26.1, 26.2, 34.4, 52.0, 60.7, 68.0, 74.2, 78.1, 79.4, 110.9; HRMS calcd for $C_{17}H_{33}NO_3Si$ (M + 1) 328.2308, found 328.2310.

(1*S*,2*R*,8*R*,8a*R*)-Octahydroindolizine-1,2,8-triol ((−)-Swainsonine (1)). To a solution of **12** (251 mg, 0.77 mmol) in THF (8 mL) was added 6 N HCl (8 mL), and the mixture was stirred at rt for 12 h. The mixture was concentrated in vacuo to dryness, and the resulting crude product was applied to ion-exchange chromatography (Dowex 50WX8−100, H^+ form, 100−200 mesh) eluting with aqueous ammonium hydroxide solution (0.6 M). Removal of water in vacuo provided **1** (110 mg, 83%) as a white solid: mp 140−142 °C; $[\alpha]^{25}_D$ −82.6 (*c* 0.5, MeOH); IR (neat) 3853, 3741, 2927, 1688, 1526, 676 cm^{-1};^1H NMR (500 MHz, D_2O) δ 1.19 (dddd, J = 4.5, 11.5, 13.0, 13.5 Hz, 1H), 1.46 (qt, J = 4.5, 13.5 Hz, 1H), 1.68 (ddd, J = 2.5, 4.5, 14.5 Hz, 1H), 1.95 (dd, J = 4.0, 9.0 Hz, 1H), 1.99 (dd, J = 3.5, 12.5 Hz, 1H), 2.01 (dq, J = 3.5, 14.5 Hz, 1H), 2.57 (dd, J = 8.0, 11.5 Hz, 1H), 2.87 (dd, J = 2.5, 11.0 Hz, 1H), 2.86−2.92 (m, 1H), 3.75 (ddd, J = 4.5, 9.5, 11.0 Hz, 1H), 4.21 (dd, J = 4.0, 6.0 Hz, 1H), 4.31 (ddd, J = 2.5, 6.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 23.0, 32.3, 51.5, 60.5, 66.2, 68.9, 69.5, 72.7; HRMS calcd for $C_8H_{16}NO_3$ (M + 1) 174.1130, found 174.1132.

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Supporting Information Available: Full spectral details and assignments and copies of the ^1H and ^{13}C NMR spectra of compounds **7**, **6**, **8c**, **8d**, **8a**, **8b**, **5**, **4**, **9**, **9′**, **3**, **2**, **11**, **12**, **1**, and precursors of **5**, **3**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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